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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,304	KATZ ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,11-29,57,58,66,69,71,81 and 84-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 11-29, 57-58, 66, 69, 71, 81, 84-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed March 21, 2003. Claims 4-10, 30-56, 59-65, 67-68, 70, 72-80, 82 and 83 have been cancelled. Currently, claims 1-3, 11-29, 57-58, 66, 69, 71, 81, 84-88 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Election/Restrictions

1. Applicant's election without traverse of Group I, Claims 1-29, 57-66, 68-82, 84-88 in Paper No. 6 is acknowledged. Prior to allowance of the claims, applicant is required to cancel non-elected subject matter from the claims.

Priority

2. This application claims priority to provisional application 60/222,811, filed August 4, 2000.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate

paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 11-29, 57-58, 66, 69, 71, 81, 84-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting loss of herterozygosity using a RPL 14 probe (SEQ ID NO: 1) as indicative of non-small cell lung cancer, does not reasonably provide enablement for detecting a loss of herterozygosity using a RPL 14 probe as indicative of <u>any</u> lung cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of identifying subjects at risk for the development of any cancer using an RPL14 gene probe to detect a loss of herterozygosity as indicative of any lung cancer.

The specification teaches a table which "provides an organized view of 12 patients suffering from lung cancer" (page 40, lines 8-10). It appears that the "a" sample from each patient is the non-tumorous bronchous, whereas the "b" sample from each patient is the tumorous sample. As seen in Table 1, each "a" sample had a

smaller percentage of deletions (page 40, Table 1). The specification teaches "initial data shows a promising correlation between the deletion percentage and survival of a patient." The specification fails to particularly articulate what the correlation between the deletion and the survival of a patient. Moreover, it is unclear whether the increase in percentage of deletion of RPL14 gene is significantly associated with tumorous tissue or whether the showing is merely "initial data" which requires further studies and analysis. Additionally, the specification teaches that an analysis of numerous dissociated tumors with their adjacent bronchi indicated that DNA probes from 3p and 10q are associated with smoking and appear to predict for the development of non-small cell lung cancer as well as overall survival (page 42, lines 24-28). The specification also teaches that "non-smokers who develop lung cancer have much higher rates of deletions, higher even than smokers and that these results are significant ($p<0.001$)" (page 43, lines 1-2).

The art namely, Shriver et al. (Mutation Research Genomics, Vol. 406, No. 1, pages 9-23, November 1998) teaches chromosome 3p is consistently deleted in lung cancer, oral squamous cell carcinoma and renal cell carcinoma (abstract). Shriver teaches isolating a gene located at 3p21.3, namely the ribosomal protein L14 gene (RPL14)(abstract). Shriver teaches that "genotype analysis of RPL14 shows that this locus is 68% heterozygous in the normal population, compared with 25% in non-small cell lung cancer (NSCLC) cell lines ($p = 0.008$)" (abstract). Shriver teaches using FISH to identify the location of the RPL14 gene (page 12, col 2). Shriver teaches that DNA from cells and cell lines derived from six matched normal and tumor samples were analyzed (page 16, col 1). Three tumors showed loss of one RPL14 allele while the

remaining three showed alterations in the length of the trinucleotide repeat (Table 3, page 16, col 1). Shriver teaches that heterozygosity of RPL14 was analyzed in squamous cell carcinoma of the head and neck (SCCHN) and the tumors exhibited normal levels of herterozygosity (page 16, col 2). Shriver teaches that the aberration of trinucleotide repeat differences was not statistically significant between lung cancer cases and race-matched controls (page 18, col 1). Shriver teaches that RPL14 is an important event in lung carcinogenesis in addition to being an informative makers for loss or alteration of the 3p21.3 critical region in cancer (page 20, col 2).

The art teaches several different types of primary lung cancer. These types include small cell lung cancer, non-small cell lung cancer and mesothelioma. As seen in Christman et al (US Pat. 5,670,314, September 23, 1997) gains and losses in chromosomes differ between non-small cell and small cell lung cancer (see Figure 3 and 4). Therefore, the analysis of one type of lung cancer is not correlative of all lung cancers.

Moreover, human ribosomal protein L14.22 gene (clone 507E08) with Genbank Accession Number AF329277 was over-expressed in gliomas. Qi (J. of Neuro-Oncology, Vol. 56, No. 3, pages 197-208, February 2000) teaches human ribosomal protein L14.22 is located on chromosome 14. Therefore, given only the arbitrary term RPL14 gene probe, it is unclear what structure is intended. The specification indicates that a RPL14 gene probe is SEQ ID NO: 1. When AF329277 and NM-003973 were blasted against each other no significant similarity was found.

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. First, the specification and the art only provide an association between non-small cell lung cancer (NSCLC) and deletion of RPL14. As seen in the art, gains and losses in chromosomes differ between non-small cell and small cell lung cancer (see Figure 3 and 4). Therefore, it is unpredictable which lung cancers are associated with deletion frequency and which cancers are not associated with the aberration. One of skill in the art would be unable to anticipate or predict which of the many cancers are associated with an aberration in hybridization of a RPL14 probe. It would require undue experimentation to analyze the broad range of cancers to determine which additional cancers, if any, are associated with the aberration. Therefore, the specification has not enabled the broad scope of the claims.

RPL14 gene probe is an arbitrary term which has been used in the art to define two different sequences. It is unclear which sequence is intended. The AF329277 Genbank Accession number has not been analyzed with respect to lung cancers. In fact, the art teaches that L14.22 is overexpressed in gliomas. Therefore, given the arbitrary term RPL14 , the skilled artisan would be unable to practice the claimed invention as a whole. The claim may be amended to recite SEQ ID NO: 1 to overcome this aspect of the instant rejection. Similarly, GC20 and PTEN/MMAC1 are arbitrary gene names. While the specification teaches GC20 is SEQ ID NO: 7, the specification does not appear to teach a sequence for PTEN/MMAC1.

With respect to Claims 57-58, 66, the specification does not specifically teach the detection of deletion of RPL14 as indicative of progression or metastasis of cancer. It is

unclear whether the mere deletion of the region is associated with metastasis and progression. Therefore, since neither the specification nor the art provides reasonable guidance to the skilled artisan how to practice the invention as broadly as claimed, the claims lack enablement for the full scope of the claims.

Moreover, with respect to Claim 69 directed to predicting lung cancer relapse by determining the loss of herterozygosity in the RPL14 gene, the specification teaches that the presence of 3p abnormalities in adjacent bronchial tissue was "strongly correlated with relapse." (page 43, lines 10-11). The p-value associated with this "strong correlation" is 0.09. A significance level of less that p=0.05 is indicative of statistical association. Therefore a p-value of 0.09 does not indicate statistical significance. Therefore, based upon the data in the specification, a statistical association between lung cancer relapse and RPL14 does not appear to exist.

With respect to GC20 gene probes and 10q22 DNA probes, and PTEN/MMAC1 gene probes, the specification does not teach the use of RPL14 in combination with each of these probes as significantly associated with lung cancer. Therefore, the skilled artisan would be required to perform additional experimentation to determine whether RPL14 in combination with each of these probes might be associated with additional types of lung cancers, the outcome of such research cannot be predicted and such further research and experimentation are both unpredictable and undue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 2, 14-15, 22, 23, 27, 57-58, 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shriver et al. (Mutation Research Genomics, Vol. 406, No. 1, pages 9-23, November 1998).

Shriver et al. (herein referred to as Shriver) teaches chromosome 3p is consistently deleted in lung cancer, oral squamous cell carcinoma and renal cell carcinoma (abstract). Shriver teaches isolating a gene located at 3p21.3, namely the ribosomal protein L14 gene (RPL14)(abstract). Shriver teaches that "genotype analysis of RPL14 shows that this locus is 68% heterozygous in the normal population,

compared with 25% in non-small cell lung cancer (NSCLC) cell lines (p = 0.008)" (abstract). Shriver teaches using FISH to identify the location of the RPL14 gene (page 12, col 2)(limitations of Claims 15). Shriver teaches that DNA from cells and cell lines derived from six matched normal and tumor samples were analyzed (page 16, col 1). Three tumors showed loss of one RPL14 allele while the remaining three showed alterations in the length of the trinucleotide repeat (Table 3, page 16, col 1). Shriver teaches that heterozygosity of RPL14 was analyzed in squamous cell carcinoma of the head and neck (SCCHN) and the tumors exhibited normal levels of herterozygosity (page 16, col 2). Shriver teaches that the aberration of trinucleotide repeat differences was not statistically significant between lung cancer cases and race-matched controls (page 18, col 1). Shriver teaches that RPL14 is an important event in lung carcinogenesis in addition to being an informative makers for loss or alteration of the 3p21.3 critical region in cancer (page 20, col 2).

While Shriver does not specifically teach identifying a subject at risk for NSCLC by detecting herterozygosity of RPL14, Shriver clearly illustrates that there is a significant difference between herterozygosity in cancer and control individuals.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the teachings of Shriver that the RPL14 locus is 68% heterozygous in the normal population, compared with 25% in non-small cell lung cancer (NSCLC) cell lines (p = 0.008) to indicate that individuals with loss of herterozygosity are more likely to have a predisposition to NSCLC. Shriver specifically teaches that RPL14 is an important event in lung carcinogenesis in addition to being an informative makers for

loss or alteration of the 3p21.3 critical region in cancer. The ordinary artisan, prior to determining a test for increased risk or predisposition to a disease, must first determine that the maker/aberration studied is differentially expressed in normal individuals versus diseased individuals. Once an aberration is determined to be significantly over represented or underrepresented in a diseased population, the information may be used to determine additional patients predisposition to the disease. Therefore, using the RPL14 maker for determining a predisposition of a subject to NSCLC would have been obvious in view of the teachings of Shriver.

Response to Arguments

The response traverses the rejection. The response asserts that "none of the rejected claims are drawn to a method of detecting cancer." The response asserts that the claims are directed to identifying a subject at risk for the development of lung cancer, method of progression or metastasis of lung cancer, predicting lung cancer relapse, and identifying individuals to be segregated from high risk lung cancer environments. This argument has been reviewed but is not convincing because the rejection acknowledges that Shriver does not specifically teach the methods of identifying a subject, however, the rejection is based on obviousness. As provided in the analysis of the obviousness rejection, "the ordinary artisan, prior to determining a test for increased risk or predisposition to a disease, must first determine that the maker/aberration studied is differentially expressed in normal individuals versus diseased individuals. Once an aberration is determined to be significantly over represented or underrepresented in a diseased population, the information may be used

to determine additional patients predisposition to the disease. Therefore, using the RPL14 maker for determining a predisposition of a subject to NSCLC would have been obvious in view of the teachings of Shriver." The response asserts that the "mere fact that Shriver examined cancerous cell lines and found that the contained deletions in RPL14 does not suggest that one would find these same lesions in non- or pre-canceorus cells." This argument has been thoroughly reviewed, but is not found persusasive because Shriver not only examines cell lines, but also examines tumor cells (page 16). Therefore, the possible discrepancy between cell lines and tumors is moot.

The response, page 7, para 1, "takes exception to the examiner's characterization of Shriver as ***teaching*** the importance of RPL14 in lung carcinogenesis." In response the response cites part a single statements which indicates additional analysis is needed to determine if functional loss of ribosomal protein RPL14 is an important event in lung and oral carcinogenesis. The entire passage reads, "Additional analysis is needed to determine if functional loss of ribosomal protein RPL14 is an important event in lung and oral carcinogenesis, in addition to being an informative marker for loss or alteration of the 3p21.3 critical region in cancer." This passage is directed to protein analysis of the RPL14 gene, not to gene probes which have been demonstrated to be important in lung cancer. Moreover, the response overlooks the preponderance of the evidence presented by Shriver which demonstrates a statistically significant association between loss of herterozygosity and

non-small cell lung cancer (p=0.008). Moreover, Shriver has observed transcriptional loss of the human RPL14 gene in lung cancer.

With respect to the "data" provided in the specification, there is no demonstration of statistical significance. Moreover, the response points to Example 6 (page 46-48 of the specification). This example is directed to using a probe for 3p21.3. This probe is not specific for RPL14, but rather contains RPL14, CD39L3, PMGM and GC20 (page 40). The specification teaches that RPL14 is SEQ ID NO: 1 and not the "probe for 3p21.3." Therefore, the analysis in Example 6 is not specific to the claimed invention. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. No claims allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Pauline Farrier, whose telephone number is (703) 305-3550.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
March 31, 2003

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